CHAPTER 11

FUTURE PROSPECTIVES

Treatment options for chronic pancreatitis


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FUTURE PERSPECTIVES

Breakthroughs in genetics
Over the past few years, breakthroughs in the field of genetic variations have broadened our understanding of the pathogenesis of recurrent acute pancreatitis and chronic pancreatitis (CP). Table 1 summarizes the identified more common genetic variants that are important to disease pathogenesis. Several genetic factors of rare gain-of-function and loss-of-function mutations associated with CP indicate an important role for trypsinogen expression, and its activation and degradation within the pancreas (for example mutations in PRSS1, PRSS2, SPINK1, CFTR, CTRC, CASR) [1,2]. The central role of trypsinogen in the pathogenesis of CP was confirmed in a genome-wide association study; a gene locus encoding both PRSS1 and PRSS2 can alter expression of the trypsinogen gene and thereby affect the susceptibility to develop recurrent acute pancreatitis and CP [3]. However, genetic variations other than in the trypsinogen pathway have also been discovered. For example, an increase in risk of developing CP was described through loss-of-function variations of the CPA1 gene (which encodes carboxypeptidase A1) in patients not consuming excessive amounts of alcohol [4]. Likewise, a variant at the CLDN2 locus (encodes claudin-2) has been strongly associated with CP, and is thought to accelerate the progression from acute pancreatitis to CP, particularly in patients with alcoholism [5]. This finding is important, given that about 15–20% of patients with acute pancreatitis develop CP, especially when alcoholism seems to be the cause of the acute pancreatitis [6]. Furthermore, we now know that so called ‘complex gene’ mutations alone, such as mutations in CTRC and CASR, are not sufficient to cause recurrent acute pancreatitis or CP. To increase the risk of developing recurrent acute pancreatitis or CP a combination with mutations in PRSS1, CFTR or SPINK1 is required [7].

The microbiome
Notably, assessing microbiome composition is of increasing importance in unravelling the role of bacteria in disease development [8,9]. In pancreatic diseases, particular changes in (salivary) flora composition are associated with CP and pancreatic cancer; these changes could act as a non-invasive biomarker in the future [9]. More research in the field of microbiomes and next-generation sequencing are needed to investigate the role that these and other potential risk factors (for example, gamma-glutamyltransferase 1 gene) have in the pathogenesis of CP and might provide new targets for diagnosis and treatment.

Smoking
Genetic variations should always be considered in the context of other important environmental factors that have a major contribution to disease development and progression, such as alcohol consumption and tobacco smoking. Although smoking has been a known risk factor for CP for more than three decades, in the past 5 years it has gained proper attention as an important contributing factor in the pathogenesis, development and progression of CP [10-12]. Several studies have shown that smoking cigarettes doubles the risk of developing CP compared with non-smokers, with an even stronger association in patients who also drink alcohol [10,11]. A large multicentre cohort study strengthens the evidence of smoking as a strong, independent and dose-dependent risk factor for CP [11]. These findings are in line with studies from Denmark and a meta-analysis from Italy including 12 studies of >1,500 patients with CP [10,12]. The results of that meta-analysis confirm the dose-dependent effect of tobacco use for developing CP: a pooled RR of 3.3 (95% CI 1.4–7.9) for smokers of one or more packs per day is reported compared with an RR of 2.4 (95% CI
<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Loss-of / gain-of function</th>
<th>Mutations</th>
<th>Possible effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRSS1</td>
<td>Trypsinogen</td>
<td>Gain-of-function</td>
<td>p.R122H / p.R122C</td>
<td>Inhibits autolysis and increased auto-activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>p.N29I / p.N29T</td>
<td>Increased stability and an enhanced auto-activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>p.A16V</td>
<td>Accelerate trypsinogen activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain-of-function</td>
<td>p.E79K</td>
<td>Increased trypsinogen activation by transactivation of PRSS2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss-of-function</td>
<td>p.A121T</td>
<td>Increased trypsine cleavage rate</td>
</tr>
<tr>
<td>CTRC</td>
<td>Chymotrypsinogen C</td>
<td>Loss-of-function</td>
<td>p.A73T / p.I64LfsX69</td>
<td>Reduces CTRC secretion and causes a near complete loss-of-function (the enzyme destroys prematurely activated trypsin)</td>
</tr>
<tr>
<td>CASR</td>
<td>Calcium-sensing receptor</td>
<td>Gain-of-function</td>
<td>R990G</td>
<td>Probably due to intracellular calcium dysregulation and recurrent trypsin activation/failed inhibition. In association with SPINK1 and CFTR variants, affect duct cell function.</td>
</tr>
<tr>
<td>CFTR</td>
<td>Transmembrane conductance regulator</td>
<td>Loss-of-function</td>
<td>F508-del / R75Q</td>
<td>The manifestation of disease depends on the severity of the mutation and homo/heterozygosity. For example: homozygotes (F508-del) have classic manifestations of cystic fibrosis and often develop CP early in life, compared to heterozygotes (carriers) have an increased risk for pancreatitis of 3 to 4 fold over the general population.</td>
</tr>
<tr>
<td>CLDN2</td>
<td>Claudin-2 locus</td>
<td>rs12688220 C</td>
<td>Mechanism is independent on trypsin activation. Is stronger associated with (alcoholic) CP than recurrent AP (probably acts as a disease modifier).</td>
<td></td>
</tr>
<tr>
<td>CPA1</td>
<td>Carboxypeptidase A1</td>
<td>Loss-of-function</td>
<td>MIM114850 (gene code)</td>
<td>Misfolding of the mutated peptides, causing stress inside of the endoplasmic reticulum. Especially prevalent in pediatric idiopathic CP</td>
</tr>
<tr>
<td>PRSS2</td>
<td>Trypsinogen</td>
<td>Loss-of-function</td>
<td>G191R</td>
<td>Mitigates trypsin activity and thereby protects against CP</td>
</tr>
<tr>
<td>PRSS1-PRSS2</td>
<td>noncoding region</td>
<td>rs10273639T</td>
<td>Reduces expression of PRSS1, reduces the risk of pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>
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0.9–6.6) for patients who smoked less than one pack per day. In addition, the authors show that smoking cessation is helpful, as the risk in current smokers is higher than in former smokers, with pooled RR estimates of 2.8 (95% CI 1.8–4.2) and 1.4 (95% CI 1.1–1.9), respectively [10]. Smoking is also associated with an earlier diagnosis of CP than non-smoking (<5 years), leading to an increased risk of developing calcifications and endocrine insufficiency [13]. Unfortunately, the mechanisms behind the pancreatic injury or how it influences the progression of the pancreatic inflammatory process are still poorly understood. Experimental studies show that cigarette smoke leads to or enhances fibrosis of pancreatic acinar cells (probably via reactive oxygen species), with an upregulation of trypsinogen and chymotrypsinogen genes. Nicotine causes further cellular injury as it results in high levels of intracellular calcium [14-16]. Similar to alcohol, smoking is an important risk factor in the development and progression to CP, but is often underestimated by physicians and patients. Physicians should educate and counsel their patients to stop smoking as they do with alcohol consumption. Lifestyle advice is an important part of the treatment.

Risk of pancreatic cancer

A significant association exists between smoking and pancreatic cancer, with a 2–3 fold increased risk of pancreatic cancer for patients who smoke [17]. The cumulative risk of pancreatic cancer in patients with CP after 10 years and 20 years is 2% and 4%, respectively [18,19]. Raimondi et al. has found an increased RR of developing pancreatic cancer of 5.1 in patients with unspecified pancreatitis, 13.3 in patients with CP and 69.0 for patients with hereditary pancreatitis in a meta-analysis that included 22 studies [20]. Patients with hereditary pancreatitis have a high cumulative lifetime risk of developing pancreatic cancer of 40–55% [21,22]. Besides smoking, obesity and dietary factors (such as high intake of red meat) are associated with an increased risk of pancreatic cancer [23-25]. These environmental factors are important for future research—especially in combination with the rapidly developing field of next generation DNA sequencing, gut and oral microbiota analyses and microRNA testing—for determining the subgroup of patients with CP at high risk of developing pancreatic cancer [9,26]. In conclusion, patients with CP have a small but increased risk of developing pancreatic cancer. Screening of patients with CP for pancreatic cancer cannot be recommended yet, as cost-effectiveness data of surveillance are lacking.

Surgery outperforms endoscopic therapy

Two randomized trials have compared endoscopy with surgery in patients with late-stage CP [27,28]. In both trials complete and partial pain relief is seen more frequently after surgery than after endoscopic treatment after 5–6 years of follow-up. A Cochrane review of endoscopic or surgical intervention for painful CP has pooled the data of both randomized trials (111 patients) [29]. A higher proportion of patients in the surgical group achieves pain relief than in the endoscopic group (partial or complete pain relief: RR 1.62, CI 1.11–2.37; complete pain relief: RR 2.45, CI 1.18–5.09).

In the randomized trial by Dite et al. surgery is superior to endoscopic therapy in terms of complete pain relief (34% versus 15%) after 5 years of follow-up in 72 patients with advanced CP [27]. The results of this trial should be interpreted with caution. The endoscopic therapy was suboptimal, as ESWL and cumulative stenting was not applied. In the surgical group, different procedures were performed including drainage, resection and combined approaches altogether. Most of the patients in this study underwent a resection procedure. The trial by Cahen et al. has
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included 39 patients with advanced CP with a follow-up of 79 months. Patients undergoing surgery have a higher rate of complete or partial pain relief, and require fewer procedures than patients undergoing endoscopic treatment [30]. Furthermore, about half of the patients in the endoscopic group still needed surgery during follow-up. Quality of life, pancreatic function, hospital stay and costs are comparable between endoscopic and surgical treatment [28,31,32].

Early intervention
Currently, a conservative step-up approach is used for the treatment of CP. Although conservative medical treatment might reduce symptoms in some patients, it does little to influence the progression of disease and symptoms in the long run. Besides smoking and alcohol cessation, various studies suggest that surgical intervention early in the disease process might mitigate disease progression, reduce pain symptoms more adequately than the conservative approach and slow down deterioration of pancreatic function in patients with CP [33-40]. Different animal studies show better morphological features and pancreatic exocrine function when early surgical drainage is performed versus late drainage[38]. Various clinical cohort studies reported stabilization and postponement of both endocrine and exocrine insufficiency after surgical drainage procedures [39-41]. Furthermore, in a small randomized trial of 17 patients with CP and dilated pancreatic duct and pain, patients who underwent early surgical intervention had markedly better pain relief as well as endocrine and exocrine pancreatic function compared with the conservatively treated group [41].

The timing of intervention remains a dilemma for those involved in the treatment of patients with CP. A large multicentre randomized trial is currently being conducted within the Dutch Pancreatitis Study Group: the ESCAPE trial (Early Surgery versus Optimal Current Step-Up Practice for CP trial; ISRCTN45877994) [42]. The ESCAPE trial will help to answer the question of whether early surgical intervention for CP improves pain control and pancreatic function compared with the current step-up practice of medical, endoscopic and finally surgical treatment in patients with CP as discussed in Chapter 9 [42].

Need for evidence-based medicine
Although surgical drainage procedures have been shown to be more effective than endoscopic drainage procedures in patients with late-stage obstructive CP, no consensus exists for the indications and timing of endoscopic or surgical intervention among gastroenterologists and surgeons. The treatment of CP is for the most part still based on local expertise, beliefs and disbeliefs and not on evidence-based medicine principles. Furthermore, it tends to be country, intraspeciality and interspeciality dependent. Some physicians believe that endoscopic therapy in CP should always be applied before surgical treatment in obstructive CP; whereas others believe that surgical drainage is more effective than endoscopic treatment in patients with obstruction of the pancreatic duct due to CP as shown in two randomized controlled trials and should be the treatment of choice in these patients [28,29,43]. It is important that patients with complex cases should be treated in expert centres by multidisciplinary teams.

It has been suggested that there are differences in type of surgery and even in morphology of the pancreas in patients with CP between countries [44]. Keck et al. compared pancreatic morphology and type of operation in 93 consecutive patients with CP operated in Freiburg, Germany and Boston, USA. Notably, the patients in Germany had a larger pancreatic head (4.5 cm versus 2.6 cm), more gastric outlet obstruction symptoms (9 of 48 and 1 of 45, respectively) and more splenic
or portal vein thrombosis compared with the patients in Boston. These finding might be because patients in Germany had a longer period of conservative therapy compared with the patients in the USA (median 56 months versus 26 months). In the Boston group, ~90% of the procedures were a pancreatoduodenectomy and in Freiburg a duodenum preserving pancreatic head resection (DPPHR) was performed in about half of the patients. These variances might reflect differences in reference between centres or differences in thoughts about timing and type of surgery; the authors also suggest that the morphology of CP differs between continents [44]. Even between surgeons there are different beliefs regarding the different surgical procedures for the treatment of CP, such as in the pancreaticojejunostomy and Frey and Beger procedures. For example, it has been suggested that drainage procedures, such as the pancreaticojejunostomy, do not solve the problem of ongoing inflammation and therefore does not provide adequate long-term pain relief in most patients, whereas the DPPHR is able to provide pain relief because it removes the root of the problem, namely the pancreatic head.

Similar to studies in the field of pancreatic cancer showing an inverse relationship between hospital volume and treatment outcome, patients with CP should also be treated in expert centres, with multidisciplinary expertise, available facilities and a dedicated team [45]. The decision of which procedure to choose should be based on evidence-based medicine and the surgeon’s experience. In patients in whom endoscopic and surgical treatments have failed to alleviate symptoms of pain, a multidisciplinary approach with consultation of pain specialists and psychologists is critical.

Conclusions
Surgery outperforms endoscopic treatment in long-term outcome of late stage obstructive CP. Patients should be treated in a multidisciplinary team in centres of excellence with expertise in medical, endoscopic and surgical treatment in chronic pancreatitis. Recent breakthroughs in the field of genetics have improved our knowledge of the aetiology and pathogenesis of CP. These new findings should be combined with our knowledge on metabolic and environmental (risk) factors, to achieve the most effective treatment for patients with CP.
REFERENCES

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